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Potential of green tea EGCG in neutralizing SARS-CoV-2 Omicron variant with greater tropism toward the upper respiratory tract

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ABSTRACT

Background: COVID-19 due to SARS-CoV-2 infection has had an enormous adverse impact on global public health. As the COVID-19 pandemic evolves, the WHO declared several variants of concern (VOCs), including Alpha, Beta, Gamma, Delta, and Omicron. Compared with earlier variants, Omicron, now a dominant lineage, exhibits characteristics of enhanced transmissibility, tropism shift toward the upper respiratory tract, and attenuated disease severity. The robust transmission of Omicron despite attenuated disease severity still poses a great challenge for pandemic control. Under this circumstance, its tropism shift may be utilized for discovering effective preventive approaches.

Scope and approach: This review aims to estimate the potential of green tea epigallocatechin gallate (EGCG), the most potent antiviral catechin, in neutralizing SARS-CoV-2 Omicron variant, based on current knowledge concerning EGCG distribution in tissues and Omicron tropism.

Key findings and conclusions: EGCG has a low bioavailability. Plasma EGCG levels are in the range of submicromolar concentrations following green tea drinking, or reach at most low μM concentrations after pharmacological intervention. Nonetheless, its levels in the upper respiratory tract could reach concentrations as high as tens or even hundreds of μM following green tea consumption or pharmacological intervention. An approach for delivering sufficiently high concentrations of EGCG in the pharynx has been developed. Convincing data have demonstrated that EGCG at tens to hundreds of μM can dramatically neutralize SARS-CoV-2 and effectively eliminate SARS-CoV-2-induced cytopathic effects and plaque formation. Thus, EGCG, which exhibits hyperaccumulation in the upper respiratory tract, deserves closer investigation as an antiviral in the current global battle against COVID-19, given Omicron's greater tropism toward the upper respiratory tract.

1. Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic has generated a catastrophic impact on public health. Various variants of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) emerge as the pandemic is continuously evolving. Variants of concern (VOCs) declared by the World Health Organization include Alpha, Beta, Gamma, Delta, and Omicron (Lino et al., 2022; Mittal et al., 2022). A considerable number of mutations in Omicron spike and its receptor-binding domain (RBD) that is responsible for binding to angiotensin-converting enzyme 2 (ACE2) result in a great increase of virus transmissibility (Dhawan et al., 2022; Islam et al., 2022; Mittal et al., 2022; Viana et al., 2022).

Abbreviations: ACE2, angiotensin-converting enzyme 2; EGCG, epigallocatechin-3-gallate; GRP78, glucose-regulated protein 78; HO-1, hemeoxygenase 1; IFN-β, interferon-β; M^{pro}, main protease; MxA, MxGTPases; Nrf2, nuclear factor erythroid 2 p45-related factor 2; Nsp15, nonstructural protein 15; TMPRSS2, transmembrane serine protease 2.

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Nowadays, Omicron has become the dominant lineage globally. Several Omicron sub-variants (BA.1-BA.3) have been identified. Among them, BA.2 appeared to have a selective advantage over others and thus caused hyper-transmissibility in several regions of the world (Fan et al., 2022; Guan & Zhong, 2022; Silva et al., 2022). Along with the emergence of new Omicron sub-variants, BA.4 and BA.5 are on the rise worldwide and are showing a tendency of replacing BA.2 (Callaway, 2022; Desingu & Nagarajan, 2022; Tegally et al., 2022). The high transmissible nature of Omicron initially raised a worldwide panic. Thus, clinical symptoms subjected to the infection received enormous attention. Early observations from South Africa and the United Kingdom suggest that Omicron appears to be less dangerous than its predecessor Delta (Jassat et al., 2022; Menni et al., 2022). Whether the attenuated clinical manifestations under the background of widespread vaccination are a protective result of the vaccine rather than an actual decrease in viral pathogenicity remains inconclusive (Brandal et al., 2021; Espenhain et al., 2021; McMahan et al., 2022). Thus, scientists have attempted to resolve the puzzle by explicitly determining Omicron pathogenicity in ex vivo/in vitro models and in unvaccinated animals.

Several groups consistently demonstrate that Omicron replicates less efficiently in human lung cells or in ex vivo explant culture of human lungs, compared with previous variants (Hui et al., 2022; Meng et al., 2022; Smith, 1972; Zhao et al., 2022). However, Omicron replication is similar to or higher than previous variants in human nasal epithelial cells (Meng et al., 2022; Pia & Rowland-Jones, 2022). These in vitro and ex vivo findings imply that Omicron has a feature of attenuated pathogenicity in the lower respiratory tract and uncompromised pathogenicity in the upper respiratory tract. Such an assumption is corroborated by a series of animal experiments. Body weight loss is a common sign that virus infections are causing severe disease in animals. Unusually, McMahan et al. observed that infection with Omicron (B.1.1.529) did not result in any detectable weight loss in hamsters, even at high challenge doses, while the infections with prior SARS-CoV-2 variants led to substantial weight loss (McMahan et al., 2022). They further noted that Omicron infection led to viral replication in both the upper and lower respiratory tracts, with higher viral loads in the nasal turbinates and lower viral loads in the lung compared with a prior SARS-CoV-2 variant (McMahan et al., 2022). Similar results were also reported by Halfmann et al. (Halfmann et al., 2022) and Yuan et al. (Yuan et al., 2022), respectively. Both groups observed that mice or hamsters infected with Omicron (B.1.1.529) had limited weight loss, reduced viral burden in the lower respiratory tract, and decreased lung pathology or clinical scores compared to those infected with previous SARS-CoV-2 variants (Halfmann et al., 2022; Yuan et al., 2022). Consistent findings were further reported by Uraki et al. (Uraki et al., 2022). They showed that all hamsters infected with Omicron BA.2 survived while all hamsters infected with a previous variant died. The lung titers in the Omicron BA.2-infected group were approximately >10,000-fold lower than those in previous variant-infected group, although all viruses replicated to similar levels in the nasal turbinates (Uraki et al., 2022). These data together strongly suggest that Omicron results in robust upper respiratory tract infection, but makes a feeble attack on the lungs (Kozlov, 2022), compared with prior variants that wreaked havoc in the lungs. These experimental results are compatible with emerging human data indicating that the prevalence of symptoms that characterize an Omicron infection differs from those of Delta, apparently with less involvement of the lower respiratory tract and reduced probability of hospital admission (Jassat et al., 2022; Menni et al., 2022).

Previous variants have exploited transmembrane serine protease 2 (TMPRSS2) to infect cells including lung cells (Hoffmann et al., 2020). Omicron spike was less efficiently cleaved by TMPRSS2 compared with Delta spike (Meng et al., 2022). Instead, Omicron tends to enter nose and throat cells deficient in TMPRSS2 via cathepsin-mediated endocytosis route (Hui et al., 2022; Meng et al., 2022; Zhao et al., 2022). The less efficient cleavage of Omicron spike results in a shift in cellular tropism away from TMPRSS2-expressing cells. The changed cellular entry pathway suggests that Omicron likely establishes a very local infection in the upper airway. The difference in entry pathway between Omicron and Delta variants (Fig. 1) may have an implication for the clinical manifestations or disease severity. The lower replication competence of Omicron in the lungs may explain the reduced severity as observed in epidemiological studies (Fan et al., 2022; Menni et al., 2022; Silva et al., 2022). The higher replication competence of Omicron in the upper respiratory tract increases the likelihood of virus release while breathing or speaking; such an upper airway preferred trait (Kozlov, 2022) helps to explain enhanced transmission through the airborne route. Despite putative decreases in the severity of the disease caused by Omicron, its hyper-transmissibility still presents a huge pressure on health care systems, and may undermine global efforts to control the pandemic. Hence, there is still an urgent need for effective preventive and therapeutic approaches.

A growing body of data demonstrates that Omicron, whose spike has undergone a pronounced mutation relative to the earliest SARS-CoV-2 isolates, can escape the immune response established by vaccination, causing a large number of breakthrough infections in vaccinated populations (Fan et al., 2022; Kuhlmann et al., 2022; Silva et al., 2022). Likewise, antibody therapies have been shown to be less effective against Omicron (Fan et al., 2022; Silva et al., 2022; Takashita et al., 2022). However, the situation seems different in terms of small-molecule antiviral drugs. Many studies have demonstrated that Omicron remains sensitive to a broad range of small-molecule antiviral drugs already approved for the treatment of COVID-19 or under investigation, such as remdesivir, molnupiravir, nirmatrelvir, favipiravir, PF-07304814, EIDD-1931, ribavirin, and Y180 (Bojkova et al., 2022; Li et al., 2022; Quan et al., 2022; Rosenke et al., 2022; Takashita et al., 2022; Vangeel et al., 2022). This suggests that key residues in the active sites of canonical drug targets including RNA-dependent RNA polymerase and the main protease (M^{pro}) in Omicron are highly conserved or do not change considerably over time.

The widespread transmission of Omicron constitutes a tremendous challenge for pandemic control. Routine vaccination or a previous infection cannot be relied upon to provide effective protection against Omicron. Booster vaccination is obligatory to generate sufficient neutralizing antibodies. Moreover, SARS-CoV-2 Omicron subvariants (BA.2.12.1, BA.4, and BA.5) continue to evolve with increasing neutralization escape in populations with high frequencies of vaccination and prior BA.1 or BA.2 infection (Hachmann et al., 2022; Wang et al., 2022). The antibody-evasive and upper airway preferred traits of Omicron led us to reconsider early reports concerning potent SARS-CoV-2 neutralization by high concentrations of green tea epigallocatechin gallate (EGCG), which could reach concentrations as high as tens or even hundreds of micromoles in the pharynx (Furushima et al., 2021; Kicker et al., 2022). Thus, we were compelled to compile available evidence amid the surge of Omicron infection, with the hope that EGCG will receive the attention it deserves in the battle against Omicron.

2. Antiviral activity of EGCG against SARS-CoV-2

Green tea, made from the leaves of the *Camellia sinensis* L. species of the Theaceae family via non-fermented processing, has been used as a crude medicine for over 4000 years in China (Cheng, 2004, 2006; Han et al., 2016). Now it is a popular beverage worldwide, especially in adults starting to focus on health concerns, because it does not have significant caloric content and yet possibly possesses multiple health-promoting effects, such as body weight control, metabolic syndrome alleviation, prevention of cancer, diabetes mellitus, and cardiovascular, neurodegenerative or infective diseases (Yang et al., 2002; Yang et al., 2016; Zhang et al., 2019; Z. Zhang et al., 2021; Zhao et al., 2020). Some green teas contain unusually high quantities of catechins (up to 35% of dry weight pending on the cultivar) including epicatechin, epicatechin gallate, epigallocatechin, and EGCG (Datta et al., 2022; Yang et al., 2002). Among these, EGCG is the most abundant (over 50%

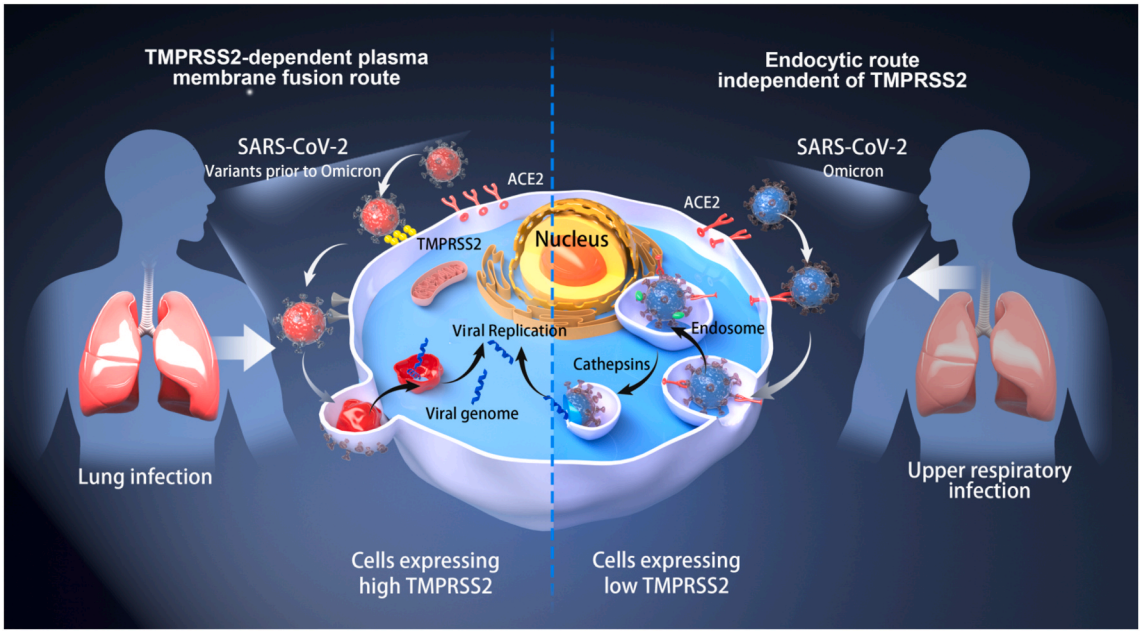

Fig. 1. A schematic illustration of cell entry pathways used by SARS-CoV-2. SARS-CoV-2 Omicron variant enters cells via an endocytic route (right), whereas the previous variants enter cells through the TMPRSS2-dependent plasma membrane fusion route (left). ACE2: angiotensin-converting enzyme 2; TMPRSS2: transmembrane serine protease 2.

in most cases) (Yang et al., 2002; Zhao et al., 2020) and is the best-documented in terms of antioxidant and prooxidant activities as well as its redox-associated biological functions (Datta et al., 2022; Dong et al., 2016; Yang & Hong, 2013).

EGCG has a broad-spectrum activity against diverse human RNA viruses including hepatitis C virus, Ebola virus, influenza A virus, human immunodeficiency virus, Zika virus, Dengue virus, West Nile virus, Chikungunya virus, and human porcine reproductive and respiratory virus, as well as various human DNA viruses such as hepatitis B virus, herpes simplex virus, and human papillomavirus (Ciesek et al., 2011; Isaacs et al., 2008, 2011; Kaihatsu et al., 2018; Kim et al., 2013; Song et al., 2005; Steinmann et al., 2013; Weber et al., 2003; Xu et al., 2008, 2017; Yamaguchi et al., 2002). A green tea catechin ointment with EGCG as the major constituent has been approved by the Food and Drug Administration (FDA) and European Medicine Agency (EMA) as a topical application drug for the therapy of external genital and anal warts – non-malignant skin tumors caused by human papillomavirus (Hara, 2011; Meltzer et al., 2009; Stockfleth et al., 2008; Tatti et al., 2010; Tzellos et al., 2011). This sole example of EGCG as a drug component involves local application of EGCG with a rather favorable safety and tolerability profile, implying that delivering high concentrations of EGCG in virus-resident site(s) is essential for successful utilization of antiviral activity of EGCG. Given that SARS-CoV-2 Omicron variant has a greater tropism toward the upper respiratory tract and that EGCG can be massively retained in the upper respiratory tract following its contact with the oral cavity (Yang et al., 1999), EGCG clearly has potential as a preventive and therapeutic agent against Omicron. Next, we have summarized advances of EGCG's effects on SARS-CoV-2 (Table 1), relevant mechanisms, as well as its drug distribution in the upper respiratory tract (Table 2) and plasma.

Ngwe Tun et al. examined the effect of full EGCG treatment, in which EGCG was present throughout all in vitro experimental procedures, on SARS-CoV-2 replication (Ngwe Tun et al., 2022). Specifically, Vero E6 cells were pre-treated with EGCG for 1 h prior to viral infection, and then were infected with SARS-CoV-2 for 2 h. After the supernatant containing virus and EGCG was removed, the cells were washed with phosphate buffered saline. The cells were then incubated with fresh medium containing EGCG. Results of quantitative real-time reverse transcription polymerase chain reaction indicated that EGCG exhibited antiviral activity. The half maximal inhibitory concentration (IC_{50}) of the full EGCG treatment was 6.5 μM and the virus replication was almost fully inhibited by EGCG at a dose of 50 μM, which had no cytotoxicity. The investigators further evaluated EGCG's effect on virus titers using a focus-forming assay; treatment with 25 and 50 μM EGCG resulted in 95% and over 99.9% decrease of virus titers, respectively, compared to virus control. Consistently, the viral N protein expression assessed by immunofluorescence assay was almost completely suppressed by the treatment with 50 μM EGCG. Overall, a full treatment with 50 μM EGCG was highly effective in suppressing SARS-CoV-2 replication (Table 1).

Different from the above full EGCG treatment, partial EGCG treatments on SARS-CoV-2 replication have also been evaluated. Three protocols were reported: i) EGCG is added to cells prior to the infection and SARS-CoV-2 is pre-incubated with EGCG prior to the infection; ii) SARS-CoV-2 is pre-incubated with EGCG prior to the infection and EGCG is added to cells after infection; iii) SARS-CoV-2 is pre-incubated with EGCG prior to the infection.

Tsvetkov et al. examined the effect of partial EGCG treatment in which EGCG was added to Vero cells prior to the infection (Tsvetkov et al., 2021). After 2 h incubation of SARS-CoV-2 and EGCG at 37 °C, the mixture was added to EGCG-exposed Vero cells, and the cells were incubated for an additional 2 h at 37 °C. Then, the supernatant containing viruses and EGCG were removed. Plaque formation was analyzed 3 days after the infection. The IC_{50} value of the partial EGCG treatment was 4.0 μM and the plaque formation was highly inhibited by EGCG at a dose of 20 μM (Table 1). Henss et al. also tested the effect of partial EGCG treatment on plaque formation but in a different way, namely, Vero cells were exposed to EGCG following infection rather than prior to infection (Henss et al., 2021). Specifically, EGCG was pre-incubated at 37 °C for 30 min with 100 $TCID_{50}$ (50% tissue culture infectious dose) SARS-CoV-2. The virus mixture was then used to infect Vero cells for 1 h at 37 °C. After removal of the inoculum, corresponding concentrations of EGCG were added to the cells. After 3 days, the cells were fixed and stained to visualize plaques. The IC_{50} value of the partial EGCG treatment was 3.8 μM and the plaque formation was fully inhibited by EGCG at a dose of 44 μM, which did not cause cytotoxicity following a 48-h incubation (Table 1). It is clear the two partial EGCG

Table 1
EGCG's effects on SARS-CoV-2 in Vero cells.

EGCG treatment protocol	Major results	Reference
Full EGCG treatment in which EGCG was present throughout all in vitro experimental procedures.	The IC_{50} of EGCG for virus replication was 6.5 μM and the virus replication was almost fully inhibited by EGCG at a dose of 50 μM, which had no cytotoxicity. Treatment with 25 and 50 μM EGCG resulted in 95% and over 99.9% decrease of virus titers, respectively. Viral N protein expression was almost completely suppressed by the treatment with 50 μM EGCG.	Ngwe Tun et al. (2022)
Partial EGCG treatment in which EGCG was added to cells prior to the infection and SARS-CoV-2 was pre-incubated with EGCG prior to the infection.	The IC_{50} of EGCG for plaque formation was 4.0 μM and the plaque formation was highly inhibited by EGCG at a dose of 20 μM.	Tsvetkov et al. (2021)
Partial EGCG treatment in which SARS-CoV-2 was pre-incubated with EGCG prior to the infection and EGCG was added to cells after infection.	The IC_{50} of EGCG for plaque formation was 3.8 μM and the plaque formation was fully inhibited by EGCG at a dose of 44 μM, which did not cause cytotoxicity after a 48-h incubation.	Henss et al. (2021)
Partial EGCG treatment in which SARS-CoV-2 was pre-incubated with EGCG prior to the infection.	The IC_{50} of EGCG for CPE was 9.4 μM and CPE was almost fully inhibited by EGCG at the doses of 25 and 50 μM. The IC_{50} of EGCG for plaque formation was 24.1 μM.	D. Zhang et al. (2021)
Partial EGCG treatment in which SARS-CoV-2 was pre-incubated with EGCG prior to the infection.	The IC_{50} of EGCG for CPE was 5.0 μM and CPE was almost fully inhibited by EGCG at the doses of 25 and 50 μM.	Tsvetkov et al. (2021)
Partial EGCG treatment in which SARS-CoV-2 was pre-incubated with EGCG prior to the infection.	The IC_{50} of EGCG for CPE was 0.6 μM.	Hurst et al. (2021)
Partial EGCG treatment in which SARS-CoV-2 was pre-incubated with EGCG prior to the infection.	The $PRNT_{50}$ of EGCG was 0.2 μM, and at 0.4 μM EGCG, viral plaque formation was fully neutralized.	Hong et al. (2021)

Table 2
EGCG concentrations in the upper respiratory tract following catechin treatment.

Catechin treatment	Major results	Reference
Volunteers drank 200 mL warm tea containing 107 mg EGCG. Then the volunteers rinsed their mouths vigorously with water 10 times in 2 min.	The initial salivary concentrations of EGCG were 10–50 μM with elimination $t_{1/2}$ values of 10–20 min.	Yang et al. (1999)
Volunteers held a solution containing 96 mg EGCG in the mouth for 2 min and then rinsed the mouth rigorously.	The saliva samples initially contained 120–300 μM EGCG and decreased to 25–65 μM after 30 min.	Yang et al. (1999)
Volunteers drank a beverage containing 28 mg EGCG without further rinsing their mouths with water.	Saliva EGCG concentrations were approximately 220, 125, and 50 μM at 10, 40, and 60 min, respectively, with C_{max} value of 270 μM and $AUC_{0–60}$ value of 8025 μM min.	Furushima et al. (2021)
Mice were treated orally with green tea extract (equivalent to 2 mg EGCG/kg), without further rinsing the mouth.	EGCG concentrations in pharyngeal mucosa were approximately 160 and 70 μM at 3 and 10 min, respectively.	Onishi et al. (2020)
Green tea extract was periodically (0, 30, 60, 90, and 120 min) applied to the mouth and throat of the volunteers via throat spray, without further rinsing their mouths with water.	Pharyngeal EGCG levels ranged between 750 and 890 μM during the first 60–120 min. One hour after the last application, pharyngeal EGCG concentration still remained at 570 μM.	Kicker et al. (2022)

protocols all support the notion that 50 μM EGCG is highly effective in suppressing SARS-CoV-2 replication as seen from the full EGCG treatment.

Zhang et al. investigated the neutralization effect of EGCG on SARS-CoV-2 (D. Zhang et al., 2021). They used a protocol excluding exposure of EGCG to cells prior to or after virus infection. EGCG was incubated with 50 $TCID_{50}$ SARS-CoV-2 at room temperature for 2 h, and then the mixture was added to Vero E6 cells to allow infection for 2 h. After the inoculum was removed, the cells were further cultured with fresh medium. The percentage of cytopathic effect (CPE) in infected cells was determined. The infected cells showed 100% CPE at 72 h after infection (hpi). The IC_{50} value of the EGCG treatment was 9.4 μM and CPE was almost fully inhibited by EGCG at the doses of 25 and 50 μM. Using the same treatment protocol, they also observed EGCG's influence on virus-induced plaque formation at 48 hpi; the IC_{50} value of the EGCG treatment was 24.1 μM (Table 1). Unfortunately, data for >25 μM EGCG were not provided. Presumably 50 μM EGCG might be highly effective based on the IC_{50} value. Tsvetkov et al. also examined the neutralization effect of EGCG on SARS-CoV-2 via CPE assessment and obtained similar results (Tsvetkov et al., 2021). In this study, EGCG was mixed with 50–200 $CCID_{50}$ (50% cell culture infectious dose) SARS-CoV-2 for 1 h at 37 °C; these virus-EGCG mixes were then added to Vero cells. After 5-day incubation at 37 °C, CPE was visually assessed via microscope. The IC_{50} value of the EGCG treatment was 5.0 μM and CPE was almost fully inhibited by EGCG at the doses of 25 and 50 μM (Table 1). Hurst et al. performed a similar experiment which produced a striking result (Hurst et al., 2021). In their study, EGCG was incubated with 60 $CCID_{50}$ SARS-CoV-2 for 1 h. Then the mixture was incubated with Vero 76 cells for 1 h. After the inoculum was removed, the cells were further cultured with fresh medium until >80% CPE was observed in virus control wells. The CPE assay via quantitation of neutral red stain showed that the IC_{50} value of the EGCG treatment was 0.6 μM in this cell line (Table 1). Concentration-dependent data were not provided, though presumably 2 μM EGCG might be fully effective based on the IC_{50}. A more pronounced result concerning the neutralization effect of EGCG on SARS-CoV-2 was reported by Hong et al. (Hong et al., 2021). In their study, SARS-CoV-2 was pre-incubated with EGCG for 30 min at 37 °C. Then, Vero cells were infected with the pre-incubated viruses for 30 min at room temperature and overlaid with 0.8% low-melting-point agarose. At 72 hpi, the cells were fixed with formalin and stained with crystal violet to count the viral plaques. This protocol is equivalent to the plaque reduction neutralization test (PRNT), which is a gold standard method for assessing neutralizing antibodies in serum or plasma induced by vaccine (Bewley et al., 2021; Roehrig et al., 2008). The $PRNT_{50}$ (half neutralization effect concentrations) value of the EGCG treatment was as low as 0.2 μM so that 0.4 μM EGCG was fully effective in neutralizing viral plaque formation (Hong et al., 2021) (Table 1).

The above sensational result with respect to the effectiveness of low-dose EGCG did not appear to be unique; LeBlanc and Colpitts reported similar results using human common cold coronaviruses: HCoV-229E (an alpha coronavirus) and HCoV-OC43 (a beta coronavirus) (LeBlanc & Colpitts, 2022). Briefly, HCoV-229E and HCoV-OC43 virions were pre-treated with EGCG for 10 min at 37 °C and then were used to inoculate infection-susceptible human hepatoma Huh7 cells or human lung epithelial A549 cells for 2 h. After the inoculum was removed, cells were overlaid with plaquing media. Infectivity was evaluated by plaquing efficiency on Huh7 cells for HCoV-229E or by immunofluorescence focus-forming assay on Huh7 cells and A549 cells for HCoV-OC43. The IC_{50} value of the EGCG treatment against HCoV-229E was 0.8 μM, and the IC_{50} values of the EGCG treatment against HCoV-OC43 was 0.6

μM in Huh7 cells and 0.5 μM in A549 cells. In all cases, 10 μM EGCG was able to fully eliminate the infectivity. Consistent with the high potency seen for 10 μM EGCG, Park et al. showed that 11–44 μM EGCG substantially suppressed OC43 protein expression by approximately 90–99% in HCoV-OC43-infected human HCT8 cells (Park et al., 2021). To support high potency as seen from low IC_{50} values, Park et al. further examined antiviral activity of EGCG in mice subjected to intranasal infection of HCoV-OC43, which is a surrogate for beta coronavirus family members including SARS-CoV-2 and a good alternative to overcome strict biosafety regulations in performing experiments with SARS-CoV-2. Significantly, they found that responses of mice to HCoV-OC43 were similar to those caused by SARS-CoV-2 Omicron variant, i.e., no mouse death and no weight loss due to infection. Following the infection, mice were treated daily with 10 mg/kg EGCG by oral administration for two weeks. Such a rather low dose of EGCG (equivalent to only 1 g green tea consumed by humans daily) reduced coronavirus RNA in the lung by roughly 70% (Park et al., 2021). It is known that mice are generally tolerant to a daily dose of 200–300 mg/kg EGCG by oral administration (Bose et al., 2008; Lambert et al., 2010; Mimoto et al., 2000; Wang et al., 2015). Thus, it is conceivable that a more powerful antiviral effect could be observed if the EGCG dose was escalated in this scenario, and it could be inferred that green tea intake by humans according to the recommendation for cancer prevention (6 cups daily, equivalent to 15–18 g green tea) (Adhami et al., 2004, 2009; Gupta et al., 2001; Mimoto et al., 2000) would be highly effective in controlling the infection of SARS-CoV-2 Omicron variant.

The above in vitro experiments unanimously suggest that exposure to 50 μM EGCG can exert a highly significant antiviral effect against SARS-CoV-2, notwithstanding the variation in inhibitory magnitude when EGCG's concentration were less than 50 μM. A possible reason may be due to differences in in vitro experimental setups. LeBlanc and Colpitts demonstrated that the effective concentration of EGCG is dependent on multiplicity of infection (MOI). They assessed the influence of MOI on EGCG effective inhibitory concentration using replication-competent vesicular stomatitis virus virions expressing green fluorescent protein and SARS-CoV-2 spike in Huh7, A549-ACE2, and lung epithelial Calu-3 cells. Depending upon cell type, the IC_{50} values ranged from 0.1 to 1.1 μM at a MOI of 0.5 and from 11.5 to 15.4 μM at a MOI of 5 (LeBlanc & Colpitts, 2022).

3. Antiviral mechanism of EGCG against SARS-CoV-2

Liu et al. examined SARS-CoV-2-inhibitory effectiveness by high-dose EGCG (50 and 100 μM) under different experimental conditions (J. Liu, et al., 2021). Pseudovirus bearing SARS-CoV-2 spike was pre-mixed with EGCG, or EGCG was added to the cell cultures before, during, or after the viral infection. The time-of-addition experiments showed that the highest viral inhibition occurred when EGCG was pre-mixed with the viruses prior to the infection (J. Liu, et al., 2021), suggesting that high-dose EGCG can block SARS-CoV-2 infection at the viral entry step. Indeed, EGCG dose-dependently attenuated the binding of full-length spike of SARS-CoV-2 or the RBD to ACE2. Of the various types of supportive evidence regarding the inhibition of engagement between spike/RBD and ACE2, 25–100 μM EGCG always exhibited a pronounced effectiveness (J. Liu et al., 2021). In addition to the direct influence, EGCG appears to disrupt the interaction of the spike with heparan sulfate (HS), thereby reducing HS-dependent RBD binding to ACE2 (LeBlanc & Colpitts, 2022). It has been demonstrated that glycocalyx HS residing on the cell surface facilitates conformation conversion of the RBD from close to open type that favors ACE2 binding, thereby potentiating viral infection (Clausen et al., 2020), whereas enzymatic removal of HS from tissues results in a loss of the RBD binding (L. Liu et al., 2021).

Coronavirus M^{pro}, also referred to as 3C-like protease, has an essential role in the life cycle of SARS-CoV-2 (Jin et al., 2020; Zhang et al., 2020). M^{pro} is a promising and well-recognized target for antiviral drug development (Jin et al., 2020; Zhang et al., 2020). Paxlovid, one of only two oral antiviral drugs against SARS-CoV-2 issued by the FDA for emergency use authorization, is comprised of the M^{pro} inhibitor nirmatrelvir and ritonavir, a cytochrome P450 inhibitor that increases the duration of action of nirmatrelvir and has no activity against SARS-CoV-2 M^{pro} (Saravolatz et al., 2022). A few studies have reported that EGCG can inhibit SARS-CoV-2 M^{pro} activity. A typical result is that of Jang et al., who showed that EGCG dose-dependently inhibited SARS-CoV-2 M^{pro} activity with an IC_{50} value of 7.6 μM, and that 40 μM EGCG resulted in approximately 90% inhibition (Jang et al., 2020). Kato et al. reported that the IC_{50} for EGCG was estimated to be 0.4 μM, and 20 μM EGCG had a considerable suppressive effect (over 95%) on M^{pro} activity (Kato et al., 2021). Despite the discrepancy in IC_{50} values, probably due to different in vitro setups of M^{pro} amount and exposure time, high-dose EGCG (up to 50 μM) should guarantee a robust inhibition.

Coronavirus nonstructural protein 15 (Nsp15) endoribonuclease confers on coronaviruses a trick of evading the host innate immune response (Deng et al., 2017; Hackbart et al., 2020; Kindler et al., 2017). Nsp15 endoribonuclease also promotes coronavirus replication through processing of the viral genome (Gao et al., 2021; Kang et al., 2007; Kindler et al., 2017). Nsp15 activity inhibition can rescue the host innate immune response and inhibit virus replication. Hong et al. showed that EGCG inhibited Nsp15 activity with an IC_{50} value of 1.6 μM; moreover 5 μM EGCG substantially and 20 μM EGCG fully inhibited Nsp15 activity (Hong et al., 2021). Overall, in the cascade of the spike-directed viral entry and the M^{pro}-mediated cleavage of replicase polyproteins into 12 mature nonstructural proteins including Nsp15 for viral replication (Fang et al., 2010), high-dose EGCG has a capacity of intercepting SARS-CoV-2 at multiple sites.

EGCG is liable to undergo autoxidation, leading to production of reactive oxygen species (ROS) and formation of EGCG quinine (Jia et al., 2022; Mori et al., 2010; Wei et al., 2016; Yang et al., 2022). Like ROS, EGCG quinone is also highly reactive and unstable (Ishii et al., 2008). EGCG quinone avidly and covalently reacts with cysteinyl thiols of proteins, forming protein-quinone adducts known as quinoproteins. Quinonization of native protein results in protein function modification or loss (Ishii et al., 2008; Jia et al., 2022; Yang et al., 2022; Zhang et al., 2017). For example, glyceraldehyde-3-phosphate dehydrogenase activity can be irreversibly inhibited by EGCG due to quinoprotein formation (Ishii et al., 2008). SARS-CoV-2 M^{pro} contains 12 cysteine residues of which Cys145 is an essential active site residue (Melo-Filho et al., 2022). Importantly, pyrogallol-derived quinone can be recognized by the catalytic site of M^{pro} which has a Cys145-His41 dyad, leading to a preferential covalent conjugation of quinone with the thiol in Cys145 (Su et al., 2021) and inactivation of M^{pro}. Accordingly, EGCG, with a pyrogallol structural motif on the B ring (Mori et al., 2010), inhibits SARS-CoV-2 M^{pro} by covalent binding to Cys145, forming a quinoprotein (Kato et al., 2021) (Fig. 2).

Prior to emergence of Omicron, we have analyzed potential protective mechanisms of EGCG against COVID-19, mainly based on pharmacologically achievable plasma EGCG concentrations (Z, Zhang, et al., 2021). In that review, i) we commented on the justification for using EGCG as an antioxidant for protecting against SARS-CoV-2 evoked oxidative stress, including the ROS burst inflicted by neutrophil extracellular traps; ii) we proposed modulation of endoplasmic reticulum-resident glucose-regulated protein 78 (GRP78) activity and expression as a potential pharmacological mechanism by which EGCG inhibits the SARS-CoV-2 life cycle; iii) we summarized well-documented protective effects of EGCG on cytokine storm-associated acute lung injury/acute respiratory distress syndrome; and iv) we gathered reported evidence demonstrating that EGCG has preventive potential against thrombosis, by suppressing tissue factor and platelet activation, vs. sepsis by inactivating redox-sensitive high mobility group box 1, and vs. lung fibrosis through augmenting antioxidant defense and inactivating NF-κB. These protective mechanisms and the immunomodulatory

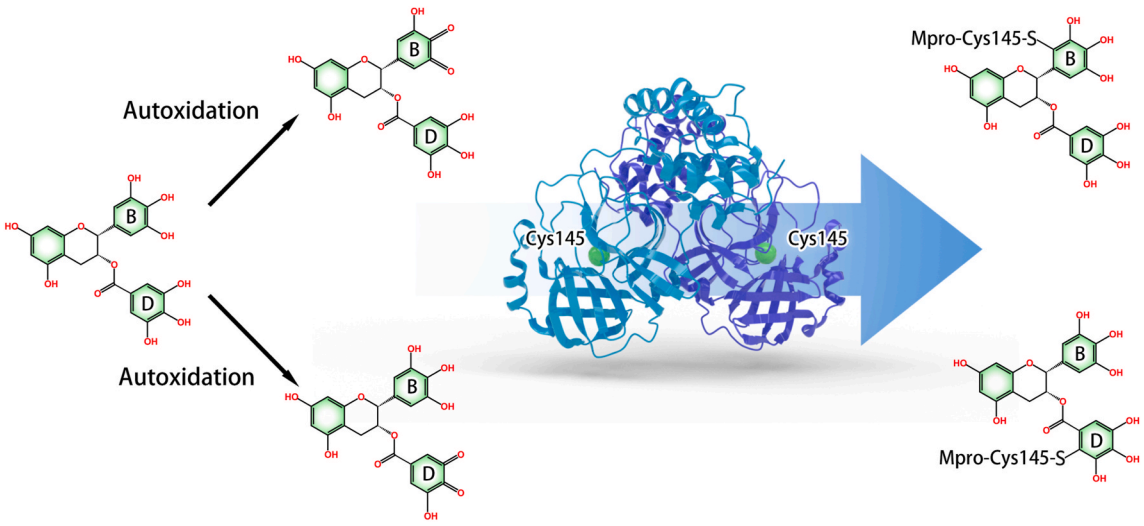

Fig. 2. EGCG inactivates M^{pro} activity via quinonization of SARS-CoV-2 M^{pro} dimer. EGCG undergoes autoxidation to form EGCG quinones in B or D ring. Catalytic site of SARS-CoV-2 M^{pro} contains a Cys145-His41 dyad. A preferential covalent conjugation of EGCG quinones with the thiol in Cys145 of M^{pro} results in quinonization of SARS-CoV-2 M^{pro} dimer, leading to inactivation of M^{pro} activity.

effects of EGCG (Tallei et al., 2021), without being addressed in more detail in the present review, suggest that EGCG could protect certain vulnerable populations such as the elderly (particularly unvaccinated older people with comorbidities) from developing severe COVID-19-associated outcomes following Omicron infection (Auvigne et al., 2022; Fan et al., 2022; Kahn et al., 2022).

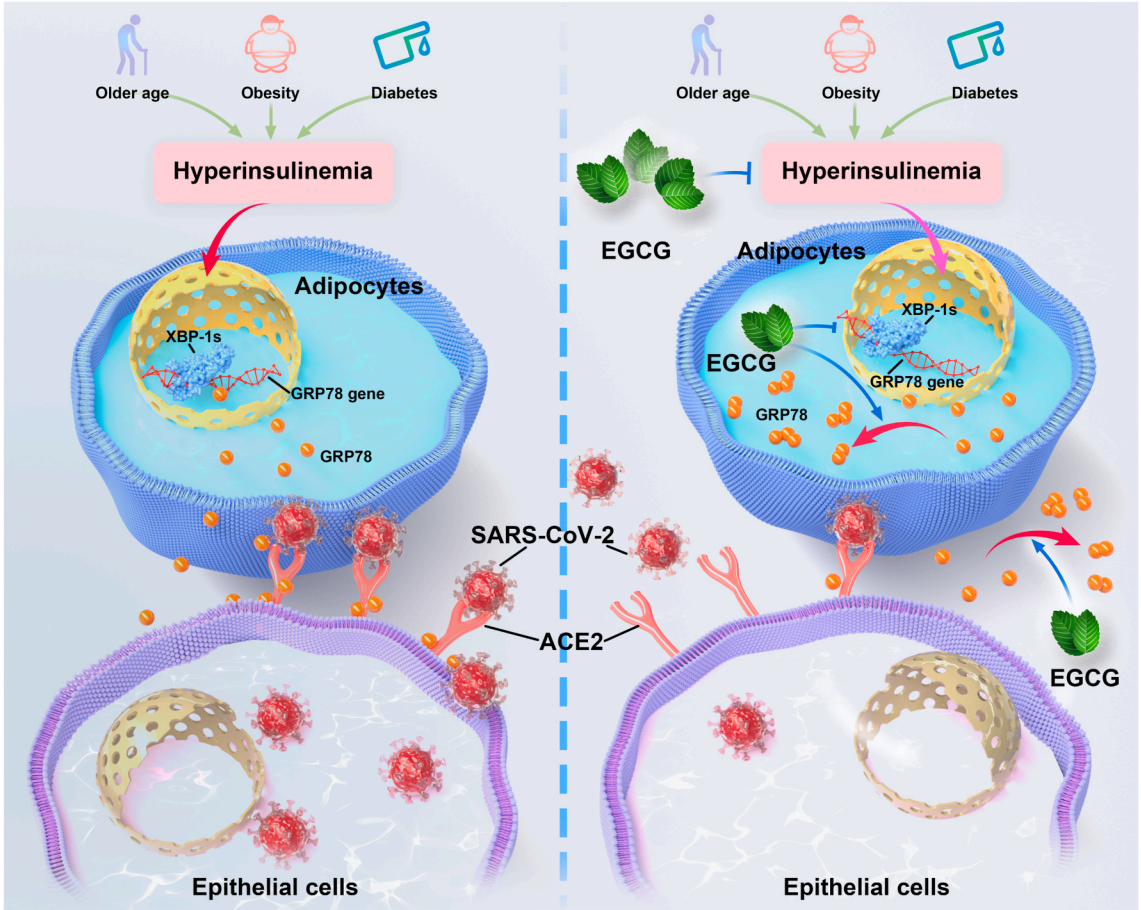

Fig. 3. Potential mechanism by which EGCG attenuates disease severity of SARS-CoV-2 Omicron infection. Hyperinsulinemia is commonly observed in individuals with advanced age, obesity and diabetes. Hyperinsulinemia induces XBP-1-mediated overexpression of GRP78 in adipose tissue, leading to increased GRP78 in the circulation. Circulating GRP78 promotes the binding of Omicron spike to ACE2 on the cell surface, resulting in more efficient cell entry of Omicron. EGCG can downregulate GRP78 protein expression. EGCG also can change GRP78 from the active monomer into inactive dimeric and oligomeric forms. In addition, EGCG has a potent ability to reduce hyperinsulinemia, which stimulates GRP78 expression.

In our previous review, GRP78 was hypothesized as a host auxiliary factor for SARS-CoV-2 entry (Z, Zhang, et al., 2021). Recently emerging studies have demonstrated that this is indeed the case. GRP78 is upregulated during SARS-CoV-2 infection and acts as a pro-viral protein (Shin et al., 2022). GRP78 can directly bind to ACE2 or the RBD of SARS-CoV-2 spike; loss of GRP78 moreover markedly reduced cell surface ACE2 expression, and a GRP78-depleting antibody is able to block SARS-CoV-2 entry and infection (Carlos et al., 2021). In addition, host-cell recognition of Omicron through GRP78 is enhanced compared with the previous variants (Elfiky & Ibrahim, 2022). This reinforces the concept that prevention strategies against Omicron infection could include the targeting of GRP78. Importantly, a recent study suggests that individuals with older age, obesity and diabetes have high levels of circulating GRP78, since GRP78 in adipose tissue, where GRP78 is highly expressed, is further increased in these populations with hyperinsulinemia, which induces stress-responsive transcription factor XBP-1-mediated overexpression of GRP78 (Shin et al., 2021). Circulating GRP78 can physically interact with SARS-CoV-2 spike or ACE2 on the cell surface, promoting SARS-CoV-2 cell entry (Shin et al., 2021). This study helps to explain why aging, obesity and diabetes are major risk factors for disease progression and more severe outcome of SARS-CoV-2 infection. These findings together suggest that EGCG is an attractive preventive agent for reducing disease severity caused by Omicron in the elderly and patients with metabolic disorders (Fig. 3), given its capacity for i) downregulating GRP78 expression, ii) changing GRP78 from the active monomer to inactive dimeric and oligomeric forms (Z, Zhang, et al., 2021), and iii) promoting remission of diabetes and hyperinsulinemia (Bose et al., 2008; Yang et al., 2016; Zhao et al., 2020).

4. Saliva EGCG concentrations and EGCG levels in the pharynx

Bioavailability of many polyphenolic compounds including EGCG and its oxidized products is relatively poor (Wu et al., 2022; Yang et al., 2008, 2016). Peak plasma EGCG only reaches a submicromolar concentration range following green tea drinking, or at most reaches low micromolar concentrations after pharmacological levels of EGCG supplementation (Chow & Hakim, 2011; Yang et al., 2008, 2016). However, EGCG concentrations in the upper respiratory tract following pharmacological intervention or green tea consumption are exceptionally high (Table 2).

An early study compared human saliva and plasma EGCG levels after the participants consumed green tea infusion and subsequently rinsed the mouth thoroughly. It was a surprise that saliva EGCG levels were two orders of magnitude higher than those in the plasma (Yang et al., 1999) (Table 2). This study further investigated saliva EGCG levels in two volunteers who held a solution containing 96 mg EGCG in the mouth for 2 min and then rinsed the mouth rigorously. The saliva EGCG was instantly increased to 120/300 μM and still remained at 25/65 μM after 30 min (Yang et al., 1999) (Table 2). Furushima et al. recently investigated the oral retention of catechins in 20 healthy volunteers following intake of a catechin-containing beverage without a rinse procedure (Furushima et al., 2021). The beverage (40 mL) contained 100 mg xanthan gum (a water-soluble polysaccharide) used to increase beverage viscosity and a total of 73 mg catechins including 28 mg EGCG. Buccal mucosa samples were collected at 10, 40, and 60 min following beverage ingestion (40 mL). The mucosa weight collected was calculated by subtracting initial swab weight from the weight of the swab after the collection. The mucosa volume was converted assuming that saliva density was 1.0. The results showed that saliva EGCG concentrations were approximately 220, 125, and 50 μM at 10, 40, and 60 min, respectively. The C_{max} (peak EGCG concentration) was 270 μM. The $AUC_{0–60}$ (area under the curve from 0 to 60 min after ingestion) was 8025 μM·min (Table 2), suggesting that a sustainable saliva EGCG concentration of over 100 μM within 1 h is available by consuming roughly 30 mg EGCG (equivalent to 0.6 g green tea). Therefore, it is conceivable that the recommended dose for cancer prevention by green tea (15–18 g) (Adhami et al., 2004, 2009; Gupta et al., 2001; Mimoto et al., 2000) is sufficient for maintaining saliva EGCG over 100 μM within a whole day. This study has a limitation because mucosa was collected from the buccal area instead of the pharynx. It is important to know the concentration of EGCG retained in the pharynx, one of the principal sites infected by SARS-CoV-2 Omicron variant.

Onishi et al. has measured EGCG levels adsorbed on the pharyngeal mucosa in mice subjected to the treatment of green tea extract (GTE) (Onishi et al., 2020). Mice orally ingested 50 μL GTE (0.05% or 0.20%) in which EGCG accounted for 56% by weight. Samples of pharyngeal mucosa were collected with swabs and the mucosa weight/volume was calculated as above (Furushima et al., 2021). GTE dose-dependently increased pharyngeal mucosa EGCG. EGCG concentrations in pharyngeal mucosa of the mice treated with 0.20% GTE were approximately 160 and 70 μM at 3 and 10 min, respectively (Table 2). Since each mouse was provided with 50 μL of 0.11% EGCG (0.20% GTE containing 56% EGCG), this dose is equivalent to 2 mg/kg EGCG. It is known that daily 200–300 mg/kg EGCG (i.g.) is safe for mice (Bose et al., 2008; Lambert et al., 2010; Mimoto et al., 2000; Wang et al., 2015). Such a safety threshold could be divided into 100–150 doses (2 mg/kg/dose) at a 10 min interval. Thus, pharyngeal concentration of EGCG could be maintained at a level around 100 μM for 17–25 h based on the concentrations at 3 and 10 min shown above (Furushima et al., 2021). These data suggest that daily high-dose EGCG within a safe range is enough for maintaining pharyngeal EGCG around 100 μM within a whole day, being similar to that obtained from saliva EGCG (Furushima et al., 2021). Kicker et al. very recently examined pharyngeal EGCG levels in six healthy adults after GTE was periodically applied to the mouth and throat via a sorbitol/lecithin-based throat spray containing concentrated GTE (Kicker et al., 2022). The throat spray was applied to the pharynx at 0, 30, 60, 90, and 120 min. Pharyngeal mucosa were collected via swabs and the mucosa weight/volume was calculated according to the above method (Furushima et al., 2021; Onishi et al., 2020). Pharyngeal EGCG levels ranged between 750 and 890 μM during the first 60–120 min. One hour after the last application, the EGCG concentration still remained at 570 μM (Kicker et al., 2022) (Table 2). These results strongly suggest that the throat spray protocol could be modified to fulfill the purpose of persistently maintaining 50 μM EGCG in the pharyngeal mucosa.

5. Nasal EGCG levels

Goblet cells on nasal mucosa secrete mucin, which absorbs water to form nasal mucus. An adult normally secretes hundreds of milliliters of nasal mucus every day. A small portion of nasal mucus is evaporated. Most of nasal mucus flows to the pharynx along the direction of cilia movement. Hitherto, nasal EGCG levels have not been reported, to the best of our knowledge. Since the posterior nasal meatus is connected with the pharynx, high concentrations of EGCG in pharyngeal fluid probably increase EGCG concentrations in nasal mucus via diffusion. However, the gravity factor due to upstream nasal mucus and downstream pharyngeal fluid may attenuate EGCG diffusion from the pharynx to the nose. Thus, a study assessing nasal EGCG levels following its intake is highly warranted, given the promising potential of EGCG against Omicron in the pharynx and throat. In the absence of such important information, we will continue to discuss this question based on another scenario, because there exists an alternative mechanism by which EGCG exerts strong antiviral activity in human nasal epithelial cells at low micromolar levels.

Emerging data indicate that nuclear-factor erythroid 2 p45-related factor 2 (Nrf2) plays an important role in protecting against COVID-19. Hemeoxygenase 1 (HO-1), a protein highly sensitive to Nrf2 regulation among numerous Nrf2 downstream proteins, has gained an increased recognition for cytoprotective effects and antiviral activity against a diverse range of viral infections (Dhawan, 2022; Singh et al., 2020; Toro et al., 2022; Wagener et al., 2020). Treatment with hemin (a

HO-1 inducer) or transient expression of HO-1 by using an expression vector efficiently suppressed SARS-CoV-2 replication (Kim et al., 2021). Nrf2 activators such as bardoxolone, bardoxolone-methyl, 4-octyl-itaconate, the clinically-approved dimethyl fumarate, and dietary sulforaphane, not only limit host inflammatory responses to SARS-CoV-2 infection, but also inhibit the replication of SARS-CoV-2. Using human nasal epithelial cells (NECs), Kesic et al. demonstrated that Nrf2 knockdown through lentiviral vectors that expressed Nrf2-specific short hairpin-RNA correlated with a significant increase in influenza virus replication in NECs (Kesic et al., 2011). EGCG is a well-recognized Nrf2 activator (Datta et al., 2022; Dong et al., 2016; Na & Surh, 2008; Yang et al., 2022; Z, Zhang, et al., 2021). The notion of an inverse relationship between levels of Nrf2 expression and susceptibility to viral infection in NECs was further corroborated by the supplementation of 1 μM EGCG in NECs. Specifically, the EGCG treatment significantly induced Nrf2 and HO-1 by 3–4 fold and suppressed virus infectivity by approximately three orders of magnitude, as evidenced by virus titer in terms of log $TCID_{50}$. It is surprising that such a physiologically achievable concentration of EGCG significantly induces Nrf2 in cultured NECs, given that higher concentrations of EGCG (25–100 μM or more) are required for Nrf2 induction in most cultured cell lines (Han et al., 2012; Hanneken et al., 2006; Kanlaya et al., 2016; Kim et al., 2022; Na et al., 2008; Shi et al., 2018; Sun et al., 2017; Wu et al., 2006; Zhu et al., 2022). This suggests that EGCG might be particularly valuable for Nrf2 induction to mitigate infection by those viruses with an upper airway tropism. The causal relationship between Nrf2 activated by EGCG and the antiviral effects of EGCG was further demonstrated by an experiment in which the virus-inhibitory action of EGCG disappeared in Nrf2 knockdown NECs (Kesic et al., 2011). Additionally, Kesic et al. found that the EGCG treatment significantly increased mRNA expression of three antiviral genes, namely, interferon-β (IFN-β), IFN-inducible MxGTPases (MxA), and retinoic acid inducible gene I (RIG-I) in NECs in the absence of virus infection (Kesic et al., 2011). IFN-β is a principal mediator of host innate immune response to virus infection. Autocrine IFN-β inhibits viral replication within the infected cells. Neighboring cells not yet infected are protected by paracrine IFN-β. Two in vitro studies have shown that IFN-β inhibits replication of SARS-CoV-2 (Clementi et al., 2020; Mantlo et al., 2020). Induction of IFN-β together with MxA and RIG-1 prior to viral infection by low micromolar concentration of EGCG primes human NECs to an antiviral state. Therefore, even if nasal EGCG concentrations could not reach the levels present in the pharynx due to likely diffusion limitation caused by gravity, the sensitive responses of Nrf2 and the induced antiviral genes to low-concentration EGCG, as well as consequent antiviral effects as seen from human NECs (the very first site of SARS-CoV-2 Omicron infection) still make EGCG an attractive prophylactic agent for mitigating Omicron infection (Fig. 4).

6. Cytotoxicity and anti-inflammatory effect of EGCG in the upper airway

Several in vitro studies suggest that EGCG has low cytotoxicity in cells originating from the upper airway. Treatment with 50 μM EGCG for 72 h did not affect viability of human nasopharyngeal epithelial cells (Fang et al., 2015). Treatment with 180 mg/L tea polyphenol (presumably containing 200 μM EGCG) for 24 h also did not affect viability of normal nasopharyngeal epithelial cells (Tian et al., 2015). On the other hand, high concentrations of EGCG can protect upper airway cells from inflammatory assaults. Mucin hyper-secretion is commonly observed in many respiratory diseases. EGCG at a concentration of 100 μM potently suppressed interleukin-1β- or phorbol 12-myristate 13-acetate-induced mucus hyper-secretion in human nasal epithelial cells (Choi et al., 2014; Kim et al., 2008). Interleukin-1β-induced inflammation, as reflected by an enormous elevation of interleukin-8 in nasal mucosal fibroblasts, was dramatically suppressed by 110 μM EGCG (Kim et al., 2006).

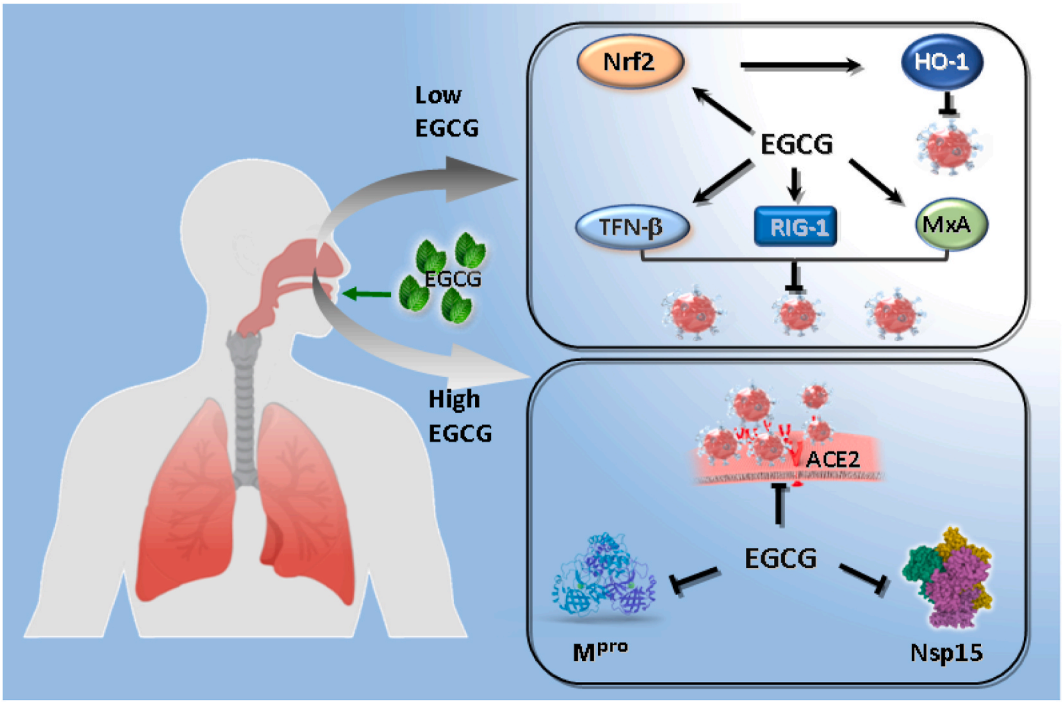

Fig. 4. Alternative protective mechanisms of EGCG against SARS-CoV-2 Omicron in the nose. EGCG concentrations in the nose may be at levels of tens to hundreds of micromolar, as is the case in the pharynx, following oral pharmacological intervention or green tea consumption. At these tissue concentrations, EGCG can effectively neutralize SARS-CoV-2 Omicron through blocking the interaction of the RBD in the spike with ACE2 and inhibiting the activity of M^{pro} and Nsp15 (the lower panel). If the EGCG concentrations are at low micromolar levels in the nose due to gravity-limited EGCG diffusion from the pharynx, EGCG is still able to exhibit strong antiviral activity against SARS-CoV-2 Omicron, via activating Nrf2, which upregulates HO-1, and via increasing expression of IFN-β, MxA and RIG-I (the upper panel). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

7. Clinical trials using catechins to prevent URTIs

Before the COVID-19 outbreak, Furushima et al. carried out a placebo-controlled, single-blind, randomized clinical trial to assess the preventive effect of catechin consumption on upper respiratory tract infections (URTIs) caused by viruses (Furushima et al., 2019). The URTIs were defined by the presence of one or more respiratory symptoms (cough, sore throat, and/or shortness of breath) and one or more systemic symptoms (≥37.8 °C, headache, malaise, and/or myalgia). The participants were randomly allocated to a placebo group (n = 86), low-dose catechin group (one daily dose of 57 mg catechins, n = 85), or high-dose catechin group (three daily doses of 57 mg catechins, n = 84). All participants consumed a beverage without or with catechins for 12 weeks. The URTI incidence rate was 26.7%, 28.2%, and 13.1% in the placebo, low-dose catechin, and high-dose catechin groups, respectively. The hazard ratio (95% confidence interval) compared to the placebo group was 1.09 (0.61–1.92) in the low-dose catechin group and 0.46 (0.23–0.95) in the high-dose catechin group. These results demonstrate that three daily doses of 57 mg catechins can protect against URTIs. It should be noted that EGCG in the three daily doses of 57 mg catechins was only 60 mg in total (equivalent to the amount in 1.2 g green tea). Provided that the recommended dose for cancer prevention (6 cups of green tea daily, equivalent to 15–18 g green tea) (Adhami et al., 2004, 2009; Gupta et al., 2001; Mimoto et al., 2000) was employed in the episode, a pronounced preventive effect on URTIs could be anticipated.

During the COVID-19 pandemic but prior to the widespread transmission of SARS-CoV-2 Omicron variant, Ozato et al. also found that a catechin-containing beverage has protective function against URTIs (Ozato et al., 2022). In this placebo-controlled, single-blind, randomized control trial over a period of 12 weeks, the catechin group (n = 55) showed significantly reduced durations of running nose, nasal congestion, and headache as well as significantly improved nasopharyngeal symptoms compared with the placebo group (n = 54). The daily intake of EGCG from the beverage was 112 mg (only equivalent to the amount in 2.2 g green tea); the achieved preventive results at that dose further support the hypothesis that high-dose green tea (15–18 g daily) or the corresponding amount of EGCG (750–900 mg daily) already being recommended for cancer prevention (Adhami et al., 2004, 2009; Gupta et al., 2001; Mimoto et al., 2000) would have considerable potential in protecting against URTIs.

Further supporting the hypothesis stated above, a systematic review and meta-analysis on preventive effects of tea and tea catechins against influenza and acute URTIs revealed a significant inverse correlation between the risk ratio and the total daily amount of catechins consumed ($p < 0.01$) (Umeda et al., 2021). Indeed, escalating the EGCG dose may lead to a strong preventive effect against URTIs, as evidenced by the report of Matsumoto et al. (Matsumoto et al., 2011). In this randomized, double-blind, placebo-controlled trial over 5 months, compared with the placebo group (n = 99), the participants (n = 98) consuming 378 mg catechins with 270 mg EGCG daily had significantly lower incidence of clinically defined influenza infection (adjusted odds ratio, 0.25; 95% confidence interval, 0.07–0.76; $p = 0.022$). In addition, the time for which the patient was free from clinically defined influenza infection as a secondary outcome was also significantly different between the two groups (adjusted hazard ratio, 0.27; 95% confidence interval, 0.09–0.84; $p = 0.023$).

An ecological study based on a global data set shows that higher green tea consumption is associated with lower COVID-19 morbidity and mortality (Storozhuk, 2022). However, an ecological study alone cannot clarify causal relationships, it can only demonstrate correlations. Thus, the association should be considered as indirect evidence supporting a hypothesis. In a study examining the association between green tea consumption and SARS-CoV-2 infection, a lower odds of infection among those who consumed high green tea consumption (≥4 cups/day) was observed, although not statistically significant, due to low sample number (Nanri et al., 2022). Hence, large-scale investigations are required. Currently, there is no randomized and placebo-controlled clinical trial to assess the preventive or therapeutic effect of EGCG on SARS-CoV-2 Omicron infection. However, a pilot study prior to the emergence of SARS-CoV-2 Omicron hints that EGCG probably effectively attenuates COVID-19 severity caused by the earlier variant of SARS-CoV-2 in humans (Bettuzzi et al., 2021). Ten SARS-CoV-2 infected patients, with the symptoms of fever >38 °C, loss of taste or smell, and respiratory or gastrointestinal problems, were treated with tea catechins daily for 15 days. The catechin administration protocol was somewhat unusual but well tolerated: it included two daily sessions of inhalation plus three capsules (total catechins: 840 mg; total EGCG: 595 mg). All participants no longer had the symptoms within 7–15 days, seven participants switched to a negative nasopharyngeal swab test within 6–13 days, and inflammation markers such as eosinophils, α-1 antitrypsin and C-reactive protein were significantly decreased. Inhaled drug delivery is the most promising administration route for the treatment of COVID-19 (Sahin et al., 2022). It is worth noting that inhaled administration of EGCG, which can provide higher EGCG concentrations to the respiratory tract without first-pass metabolism, was included in this study. The impressive results reported in this study may be closely associated with the inhaled administration of EGCG, whereas swallowing the capsules may play the least role, given poor systemic bioavailability of oral intake of EGCG. It now evident that EGCG can be retained in the pharynx and throat at very high concentrations following green tea drinking or EGCG treatment in the oral cavity; thus, this pilot study implies that green tea drinking or EGCG treatment in the oral cavity probably is particularly effective for prevention against infection by SARS-CoV-2 Omicron variant with greater tropism toward the upper respiratory tract.

8. Concluding remarks

COVID-19-associated severe outcomes post-infection by SARS-CoV-2 Omicron variant are lower compared with those caused by infection with previous variants; however, such a significant difference in COVID-19 severity is less marked in the elderly (Auvigne et al., 2022). Controlling the high volume of Omicron infection that is straining public health care systems and suppressing its resurgence are highly challenging issues globally. The World Health Organization has recommended drugs for people with severe COVID-19 disease or at risk of hospitalization; however, it does not recommend what to take for those with mild COVID-19 disease. Treatments for mild disease are helpful for i) recovering from the disease quickly, ii) reducing the risk of disease progression, iii) restraining disease spread, and iv) reducing opportunities for mutation of the virus. Owing to these benefits, scientists have started to hunt for drugs to treat those at lower risk (Sidik, 2022). Since SARS-CoV-2 Omicron variant exhibits a tropism shift toward the upper respiratory tract, in this prospective review, we have focused on analyzing potential protective effects of EGCG against Omicron. Convincing data suggest that 50 μM EGCG, which could be retained in the pharynx and throat by green tea drinking, holding EGCG in the mouth, or EGCG throat spray, can effectively neutralize SARS-CoV-2 and almost completely eliminate SARS-CoV-2-induced cytopathic effects and plaque formation, via inhibiting the engagement of the spike/RBD with ACE2, as well as the activity of M^{pro} and Nsp15. In addition, EGCG is a pleiotropic molecule able to suppress oxidative stress, endoplasmic reticulum stress, cytokine storm, thrombosis, sepsis, and lung fibrosis, and thereby very likely able to mitigate the severity of COVID-19, as outlined in our previous review (Z, Zhang, et al., 2021). Recognition of the robust in vitro effectiveness of EGCG and the myriad mechanisms by which EGCG might benefit individuals infected by Omicron (Fig. 5) provides a strong rationale for randomized, controlled trials to evaluate EGCG as a prophylactic agent against Omicron, especially in the elderly, the frailest population. Prior to human intervention studies, the optimization of mode of delivery and the corresponding dose by which high

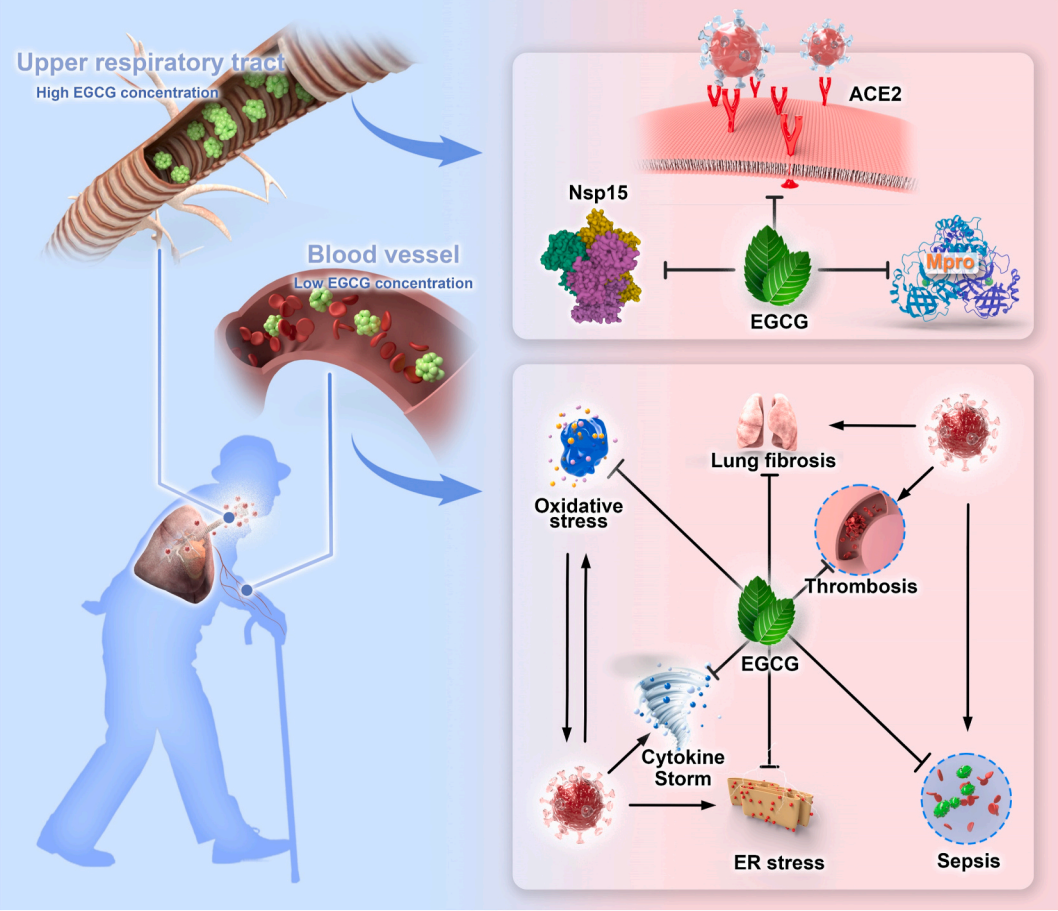

Fig. 5. Potential protective mechanisms of EGCG against SARS-CoV-2 Omicron. EGCG by oral administration could be retained in the pharynx and throat at levels as high as tens to hundreds of micromolar concentration, which are two orders of magnitude higher than that in the plasma (submicromolar to low micromolar concentrations). High levels of EGCG (tens to hundreds of micromolar concentrations) in the upper respiratory tracts can effectively neutralize SARS-CoV-2 and almost completely eliminate SARS-CoV-2-induced cytopathic effects and plaque formation, via inhibiting the engagement of the spike/RBD with ACE2, as well as the activity of M^{pro} and Nsp15. Low levels of EGCG (submicromolar to low micromolar concentrations) in the circulation are helpful for suppressing oxidative stress, endoplasmic reticulum stress, cytokine storm, thrombosis, sepsis, and lung fibrosis caused by SARS-CoV-2 Omicron in frail populations.

concentrations of EGCG are sustainable in the nose, pharynx, and throat need to be investigated as expeditiously as possible.

Author contributions

Conception of idea: J.Z. Design of review outline: X.C., E.W.T. and J. Z. Sourcing literature of clinical symptoms and molecular pathology of SARS-CoV-2 Omicron: Z.Z., X.C. and E.W.T. Sourcing literature of EGCG and tea: Z.Z., M.H., X.Z., Y.H. and J.Z. Drafting the article: Z.Z., M.H., X. Z. and J.Z. Preparing the figures: Z.Z., M.H., X.Z. and J.Z. Reviewing and revising the manuscript: X.C., E.W.T. and J.Z. Editing the manuscript: M. H.

Declaration of competing interest

The authors declare no conflict of interest.

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